# FORMULATION AND EVALUATION OF ORO DISINTEGRATING TABLETS OF SALBUTAMOL SULPHATE

A Dissertation Submitted to

**THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSTIY, CHENNAI**

*In partial fulfillment for the award of degree of*

**MASTER OF PHARMACY**

**IN**

**PHARMACEUTICS**

Submitted by

**Reg. No.: 26107710**

**Under the Guidance of**

**Ms. R. Devi., M.Pharm,**

**Asst. Professor,**

**Department of Pharmaceutics**

**ANNAI VEILANKANNI'S PHARMACY COLLEGE**

**SAIDAPET, CHENNAI – 600 015.**

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## DECLARATION

I hereby declare that the dissertation work entitled "**FORMULATION AND EVALUATION OF ORO DISINTEGRATING TABLETS OF SALBUTAMOL SULPHATE**" is based on the original work carried out by me in AnnaiVeilankanni's Pharmacy College, Saidapet, Chennai and Formulation R&D, Bright labs pharma research centrePvt Ltd., Hyderabad under the guidance of **Ms. R. Devi.,** and **G. Anil Kumar,** for submission to The TamilnaduDr.M.G.R University in the partial fulfillment of the requirement for the award of degree Master of Pharmacy in Pharmaceutics. The work is original and has not been submitted in part or full for any other diploma or degree of this or any other university. The information furnished in this dissertation is genuine to the best of my knowledge and belief.

Chennai,

21.08.2012 **26107710**

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ANNAI
VEILANKANNI'S
Pharmacy College

Dr. S.DEVARAJ
Chairman

81/33, V.G.P. Salai,
Saidapet,
Chennai - 600 015.
Landline: +91-44-4352 3712, 2485 1172,
Fax: +91-44-2471 0820.
E-mail: dev@annaiveilankannis.com,
Website: www.annaiveilankannis.com

Chennai,
21.08.2012.

## CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF ORO DISINTEGRATING TABLETS OF SALBUTAMOL SULPHATE**" submitted by **KAMMILI SUDHEER(26107710)** in partial fulfillment of the degree of Master of Pharmacy in Pharmaceutics of The TamilNadu Dr.M.G.R Medical University, Chennai at AnnaiVeilankanni's Pharmacy College, Chennai- 600 015 is the Bonafide work carried out by him under my guidance and supervision during the academic year 2011-2012. The dissertation or any part of this has not been submitted elsewhere for any other degree.

GUIDE
Ms. R. Devi., M.Pharm,
Asst.Professor,
Dept. of Pharmaceutics,
AnnaiVeilankanni's Pharmacy College,
Chennai-600015

Dr. M. Senthil Kumar, M.Pharm,Ph.D.,
Principal & Head of the
Dept. Pharmaceutics,
AnnaiVeilankanni's Pharmacy College,
Chennai-600015.

BRIGHT LABS

Pharma. Research Center Private Ltd.

Date:23/07/2012

# CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF ORO DISINTEGRATING TABLETS OF SALBUTAMOL SULPHATE** " that is being submitted by Mr. **KAMMILI SUDHEER** in partial fulfillment for Master of Pharmacy in Pharmaceutics to **THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY,** CHENNAI, is a record of bonafide work carried out by him in our research laboratory under my guidance. The results embodied in this dissertation have not been submitted to any other university or institute for the award of any degree.

G. Anilkumar M.pharm
Bright Pharmaceutical Research
Labs Hyderabad

Office: 5-70, First Floor, Near Andhra Bank, Street No.2, Ashta laxmi Arch, Hyderabad-500007
Mobile No:+91 9908521114, +91 9703596056 Email: ambatimahe@gmail.com

## 1. Introduction:

Orally disintegrating tablets (ODTs) rapidly disintegrate in the mouth without chewing upon oral administration and without the need for water, unlike other drug delivery systems and conventional oral solid immediate-release dosage forms. ODT dosage form; also commonly known as fast melt, quick melts, fast disintegrating and orodispersible systems have the unique property of disintegrating the tablet in the mouth in seconds.[1] For acute conditions, this dosage form is easier for patients to take anytime, anywhere those symptoms occur. For chronic conditions, it is assumed to improve compliance. Some important advantages of ODT drug delivery over others are ease of swallowing for patients and convenience of taking the medication anytime without the need of water. Some limitations include difficulty in developing extremely high doses (typically in excess of 500mg) and sometimes-extensive taste masking of bitter tasting actives.[2]

Orally disintegrating dosage forms are often formulated for existing drugs with an intention to extend the patent life of the drug through product differentiation. They are evaluated against the innovator drug in a bioequivalence study in humans to establish comparability of pharmacokinetic parameters. Drug delivery systems are technologies that transport the active drug into the body's circulatory system. Drug can be delivered into the body by various means, depending on its physical and chemical properties. Some may alter the method of taking the drug; others alter the desired therapeutic activity.[3]

The advent of new drug delivery systems can clearly differentiate a drug product in today's highly competitive pharmaceutical market. To better understand the concept of the drug delivery system, one needs to know how a drug delivery system can be a valuable and cost effective life cycle management resource.[4] Pharmaceutical companies worldwide have recognized various drug delivery systems as powerful marketing tools to differentiate products, extend product life cycles, and even improve the efficacy of a drug. Several example include Claritin ODTs, Actiq (transmucosal dosage form for patient compliance), and Cardiazem XL (osmotic dosage form for extended release).[5, 6] The drug delivery market encompasses a wide array of technologies that cover various routes of administration such as oral, nasal, transdermal and inhalation.

The oral route remains most popular owing to the ease of administration, manufacturing and regulatory strategy. The increasing popularity of orally disintegrating dosage forms is in part owing to various factors such as patient preference and life cycle management. Some reasons for patient preference include fast disintegration, good mouth-feel, easy to handle, easy to swallow, and effective taste masking (for tablet based technologies).[8] A perceived benefit for ODT is the ease of administration to elderly and pediatric populations and other patient populations that have difficulty swallowing traditional tablets or capsules.

A customer study was done to measure consumer/patient reactions to fast dissolving tablets. The population size was 5000 and spanned across a diverse age group. Patients were given a conventional tablet and an ODT and asked various questions. A significant majority of the patients said they ‘‘would or might’’ prefer a fast dissolve dosage form over a regular tablet or liquid. Only 12% of the patients rejected fast dissolve tablets. Most of the patients also indicated that they would ask their doctor for a fast dissolve version and would purchase a fast dissolve if available.[9]

Life cycle management allows for differentiation of product in the market. According to data monitor, drugs worth $37 billion will lose patent protection between 2000 and 2010.Development of an ODT formulation within the patent expiration period can add significant patent life to the formulation as it cannot be substituted at the pharmacy counter until an equivalent ODT is available in the market.[10]

**1.1. Manufacturing methods:**

The processes described hereunder are utilized to develop ODTs, depending on its capabilities and limitations, in addition to developing the product within an acceptable period of time satisfying all the specific needs of the product. Each technology utilizes one or more combinations of processes described below to develop ODT drug delivery systems. ODT development consists of three parts[1]

1. Evaluating the need to taste mask the drug.

2. Incorporating the taste masked/non-taste masked drug into the tablet matrix.

3. Packaging.

**Taste masking:**

Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation. The approaches are as follows.[12]

- Layering the drug onto inert beads using a binder followed by coating with a taste- masking polymer.
- Granulating the drug and coating with a taste masking polymer.
- Spray drying the drug dispersed or dissolved in a polymeric solution to get taste- masked particles.
- Complexation by the use of inclusion in cyclodextrins.
- Psychological modulation of bitterness.

**Layer/coat process:**

The layering process involves deposition of successive layers of an active compound onto the granules of the inert starter seeds such as sugar spheres or microcrystalline cellulose beads. Sugar spheres (Non Pareil) or microcrystalline spheres (Celpheres) can be used as initial substrate in the preparation of beads by the layering process.

In the layering process, the bitter drug is dissolved or dispersed in an aqueous or non-aqueous solvent, depending on its solubility characteristics and ease of processing. Binder is added to the solution to form liquid bridges between the primary particles.[13]

The various polymers used for taste-masking purpose are Eudragits, ethylcellulose, hydroxyl propyl methyl cellulose, hydroxyl propyl cellulose, polyvinyl alcohol and polyvinyl acetate. The polymer is dissolved in an aqueous or non-aqueous solvent depending on its solubility characteristic and anti-tack agents such as talc, magnesium stearate are added to improve processing and prevent agglomeration.[14]

Sometimes taste masking is possible by combining layer/coat in a single process, i.e., incorporating the drug in solution/suspension form containing a

polymer that serves both as a binder and as a taste-masking agent and then depositing the drug onto beads.[12]

**Granulation:**

Taste masking by granulation is achieved by decreasing the surface area of the drug by increasing its particle size. The additional benefit obtained is ease of processing for tablet compression as the majority of drugs have a low bulk density. Additionally, polymers that serve as binders and taste-masking agents may be incorporated, which reduce the perception of taste. Granulation may be achieved with or without the use of a solvent. Dry granulation involves the use of forming compacts/slugs that are milled for blending. Wet granulation can be achieved by using the fluid bed process or high-shear granulation. In the fluid bed process, the drug is suspended in the bed with air, and a binder is sprayed from the top. The granules formed are porous and not amenable to further processing like coating. In high-shear granulation, the granule formation occurs by spraying a liquid binder onto drug/mixture of drugs with excipients that are being agitated by combined action of an impeller and chopper. The granules obtained are dense and may be used directly or coated further in a fluid bed. This approach is suitable for high-dose drugs (>50mg) with unpleasant taste.[14]

**Spray drying:**

For taste-masking application, the drug is either dissolved or dispersed along with bulking agent (polymer) and occasionally, a binding agent is also added if required, in a suitable solvent. Spray drying consists of four stages: atomization of feed into a spray, spray–air contact (mixing and flow), drying of spray (moisture/volatiles evaporation) and separation of dried product from the air. The solvent used for spray drying process may be aqueous or non- aqueous. Product obtained upon spray drying yields high porosity granules or beads containing encapsulated drug.[14,15]

**Complexation:**

Taste masking by inclusion complexation is possible by physically entrapping the drug in cone shaped structures known as cyclodextrins. Cyclodextrins are bucket shaped oligosaccharides produced from starch. Owing to their peculiar structure and shape, they possess the ability to entrap guest molecules in their internal cavity. Drug inclusion complexes can be formed by a variety of techniques that depend on the property of the drug, the equilibrium kinetics, other formulation ingredients, processes, and the final dosage form desired.

In all these processes, a small amount of water is required to achieve thermodynamic equilibrium.[14] The initial equilibrium to form the complex is very rapid; the final equilibrium takes a longer time. The drug, once inside the cyclodextrin cavity, makes conformational changes so as to attach itself to the complex and to take maximum advantage of the weak Vander Waals forces.

Complexation is also possible through the use of ion-exchange resins. Both anionic and cationic types are available. The preparation of the taste-masked complex involves suspending the resin in a solvent in which the drug is dissolved. For liquid preparations, the drug–resin complex can be used as it is. For solid dosage forms, the complex may be processed by filtration or direct drying. Drug loading up to 50% is possible with this process. Some commercially available ion-exchange resins that may be used for taste masking are based on methacrylic acid and divinylbenzene and styrene divinyl benzene polymer.[14,16]

**1.2. Orodispersible tablets:**

Regardless of different advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance.[1]

Recently fast dissolving drug delivery systems have started gaining popularity for the reason of speedy disintegration or dissolution, self administration even without water or chewing. This can be achieved by various conventional methods like direct compression, wet granulation, molding, spray drying, freeze drying and sublimation. Some patented technologies are also there to formulate this dosage form such as Zydis technology, WOWtab technology, Orasolv technology,

Durasolv technology, Flashdose technology, Flashtab technology, Oraquick technology, Quick-Dis technology and Nanocrystal technology. For masking the obnoxious taste of the drug different polymers are brought into play for coating, different resins utilized for complex formation, sweeteners and flavors draw on in direct compression while formulating this form of delivery system.[15]

More than 50% of pharmaceutical products are orally administered for several reasons. This route of administration is considered as the most widely used route as it offers advantages like ease of administration, versatility, patient compliance and accurate dosing. Undesirable taste is one of the important formulation problems that are encountered with such oral products. Difficulty in swallowing is also a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with these groups. [17]

Faster onset of action may be very valuable for faster relief. A liquid dosage form, like a solution or dispersion will be suitable for faster action; masking the taste of a bitter drug and improving the rate of dissolution of less soluble drug become important considerations in liquid formulations.[18]Also, it is well known that liquid dosage forms, suffer from the drawbacks of inaccuracy of dosage and inconvenience of transportation and handling. Hence considering all the above points the solid dosage form, which can be administered or swallowed as a liquid, where in the bitter taste of drug is masked, would be a very ideal dosage form. One such approach is fast mouth dissolving tablet.[19,20]

Fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems which aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. Their growing importance was underlined recently when European Pharmacopoeia adopted the term “Oro-dispersible tablet” as a tablet that to be placed in the mouth where it disappears rapidly before swallowing.[21]

Mouth dissolving drug delivery system emerged from the desire to provide the patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and gelatin capsules. Hence they do not comply with prescription, which results in non-compliance and ineffective therapy.

In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Pediatric and geriatric patients experience particularly this difficulty. Such problems can be resolved by means of mouth dissolving tablet.[22]

When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

**Desired criteria:**

Mouth dissolving tablet should[23]

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature. The several advantages of fast dissolving dosage forms are
- Ease of administration for patients, those who are not co-operative.
- Quick disintegration and dissolution of the dosage form.
- Can be swallowed without water.
- Allows high drug loading.
- Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.[23]

**1.3. Technologies used for preparing ODTs:**

Various techniques used for preparing mouth dissolving tablets are freeze drying, molding, sublimation, spray drying, mass-extrusion and direct compression. Patented technologies for mouth dissolving tablets are Zydis technology, Durasolv technology, Orasolv technology, Flash dose technology, WOW technology, Flash tab technology, Ora-quick technology, Quick-Dis Technology and Nano-crystal Technology.

**Freeze drying:**

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation.

The influence of various formulation and process parameters on the characteristics of rapidly disintegrating tablets in freeze dried form is investigated by scientists who concluded that maltodextrins are useful in the formulation of fast dissolving tablets made by freeze drying.[24]

**Molding:**

Tablets produced by molding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent; it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix.

It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution.

No-vacuum lyophilization is another process which involves the evaporation of a solvent from a drug solution or suspension at standard pressure.[24]

**Sublimation:**

Compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets exhibit good mechanical strength and dissolve quickly. Inert solid ingredients (e.g. urea, ammonium carbonate, camphor, naphthalene) are added to other tablet excipients and the blend is compressed into tablet.

Removal of volatile material by sublimation generated a porous structure.[24]

**Spray drying:**

Highly porous and fine powders can be produced by spray drying process, as the processing solvent is evaporated rapidly during spray drying. For fast dissolving tablets, they developed formulation by using mannitol as bulking agent, hydrolyzed and non-hydrolyzed gelatin as support matrix, sodium starch glycolate as disintegrant and acidic material (e.g. citric acid) and/or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. When immersed in an aqueous medium, the tablets compressed from spray-dried powder, disintegrated within 20 secs.[27]

**Mass extrusion:**

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol (PEG) using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

**Direct compression:**

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually

required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling, tablet rupture during the opening of blister alveolus all results from insufficient physical resistance.[27]

Disintegrants have major role in the disintegration and dissolution process of mouth dissolving Tablets made by direct compression. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important.

Other formulation components such as water-soluble excipients or effervescent agents can further enhance dissolution or disintegration properties. But main drawback of using effervescent excipients is their highly hygroscopic nature. [1]

The understanding of disintegrant properties and their effect on formulation has advanced during last few years, particularly regarding so called super-disintegrants. Disintegration efficiency is based on force equivalent concept, which is the combined measurement of swelling force development and amount of water absorption. Force equivalent expresses the capability of disintegrant to transform absorbed water into swelling force. The optimization of tablet disintegration was defined by means of disintegrant critical concentration. Below this concentration, the tablet disintegration time is inversely proportional to disintegrant concentration and above that disintegration time remains approximately constant or even increases. [3]

**Patented technologies: Zydis technology:**

Zydis, the best known of the fast-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 secs.[28]

The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pregastric absorption from this formulation. Buccal, pharyngeal and gastric regions are all areas of absorption of the Zydis formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability.[28]

While the claimed increase in bioavailability is debatable, it is clear that the major advantage of the Zydis formulation is convenience. The amount of drug that could be incorporated should generally be less than 60mg for soluble drugs. The particle size of the insoluble drugs should be less than 50mm and not more than 200mm to prevent sedimentation during processing. There are some disadvantages to the Zydis technology. The process of freeze- drying is a relatively expensive manufacturing process. The Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidities.[28]

**Orasolv technology**:

Orasolv was Cima's first fast-dissolving/disintegrating dosage form. The Orasolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a fast disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the OraSolv formulation is two-fold. The unpleasant flavor of a drug is not merely counteracted by sweeteners or flavors; both coating the drug powder and effervescence are means of taste masking in Orasolv. This technology is frequently used to develop over-the-counter formulations.[29]

The major disadvantage of the Orasolv formulations is its mechanical strength. The Orasolv tablet has the appearance of a traditional compressed tablet. However, the Orasolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. Lyophilization and high degrees of compression, as utilized in Orasolv's primary competitors, may disrupt such as taste masking approach. The Orasolv technology is utilized in six marketed products. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0gr of drug have been developed.

Their disintegration time is less than 30secs. The Orasolv formulations are not very hygroscopic.[30]

**Durasolv technology:**

Durasolv is Cima's second generation fast-dissolving/disintegrating tablet formulation. Produced in a fashion similar to Orasolv, Durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. Durasolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The Durasolv product is thus produced in a faster and more cost-effective manner. Durasolv is so durable that it can be packaged in either in traditional blister packaging, pouches or vials.[30]

One disadvantage of Durasolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike Orasolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the Durasolv technology is best suited for formulations including relatively small doses of active compound.[30]

**Flash dose technology:**

Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ chew, require some chewing. The Flashdose technology utilizes a unique spinning mechanism to produce a floss- like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue.[30]

**WOWtab technology:**

The WOWtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. WOWtab technology is patented by Yamanouchi Pharmaceutical Corporation. The WOW in WOWtab signifies the tablet is to be given "With Out Water".

It has just recently been introduced into the U.S. The WOWtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide (good binding property). The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. Due to its significant hardness, the WOWtab formulation is a bit more stable to the environment than the Zydis or Orasolv. It is suitable for both conventional bottle and blister packaging.

The taste masking technology utilized in the WOWtab is proprietary, but claims to offer superior mouth feel due to the patented Smooth melt action. The WOWtab product dissolves quickly in 15secs or less.[30]

**Flashtab technology:**

Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of

excipients prepared by wet or dry granulation and compressed into tablets. All the processing utilized the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.[28]

**Oraquick technology:**

The Oraquick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouth feel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking.

Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics and anti-infectives.[30]

**Nanocrystal technology:**

For ODTs, Élan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology.

NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

NanoCrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally regarded as safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small

quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending and tabletting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into ODT dosage forms because manufacturing losses are negligible.[30]

**1.4. Evaluation of Orodispersible tablets: Weight variation:**

Tablets are designed to contain a specific amount of drug in a specific amount of tablet formula; the weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug.

Average weight of 20 tablets is calculated using an electronic balance. Individual weight of each tablet is calculated and compared with the average weight. The tablets meet USP specifications if no more than 2 tablets outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.[31]

**Hardness:**

Tablet hardness has been defined as "the force required to break a tablet in a diametric compression test". To perform this test, the tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded.

Hardness is thus sometimes called as "tablet crushing strength". Several devices that commonly serve the purpose of determining the tablet hardness are the Monsanto tester, the Strong-Cobb tester, the Pfizer tester and the Erweka tester.

**Friability:**

Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets, tend to "cap" on attrition losing their crown portions. Therefore another measure of tablets strength, its friability is often measured.

The laboratory friability tester is known as the Roche Friabilator. This device subjects a number of tablets to the combined effects of abrasion and shock by

utilizing a plastic chamber that revolves at 25rpm, dropping the tablets from a distance of 6 inches with each revolution.

Normally a preweighed tablets sample is placed and rotated at 25rpm for 4mins or 100rpm for 1 min using a Roche Friabilator. The tablets were then reweighed after dusting and the percentage of weight loss was calculated. The percentage weight loss usually should not exceed 0.5-1%. When capping is observed on friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss observed.[32]

**Wetting time and water absorption ratio:**

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10-cm diameter were placed in a petridish with a 10-cm diameter. Ten milliliters of water containing a water-soluble dye was added to the petridish. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time.

To check for reproducibility, the measurements were carried out (n=6) and the mean value was calculated.[27]

The weight of the tablet before keeping in the petridish was noted ($W_b$). The wetted tablet from the petridish was taken and reweighed ($W_a$). The Water absorption ratio, R, was determined according to the following equation:

$$R = 100 *(Wa - W_b) / W_b$$

Where $W_b$ and $W_a$ are the weight before and after water absorption respectively.

**Assay:**

Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to about one dose of the drug into a suitable container. Add some amount of diluting fluid in which the drug gets completely dissolved or gets extracted, stir by mechanical means until the drug gets into the solution, the solution is made up to the volume by diluting fluid and mixed well. The container is kept aside for some time until all the suspended particles get

settled. The clear supernatant is separated and filtered through membrane or cellulose acetate filter.

The drug solution obtained is diluted if necessary with the diluting fluid and checked for its absorbance using spectrophotometer. The concentration of the drug is obtained from the standard graph and the average amount of drug in the tablets was estimated.[27]

**Disintegration time:**

ODTs should be strong enough to survive rough handling during manufacturing and shipping processes and yet friable enough to instantly dissolve or disintegrate into small particles for easy swallowing by the patient. Conventional disintegration tests for ordinary tablets may not allow precise measurement of the disintegration time of FDTs because of their fast disintegration. It is also hard to distinguish among ODTs, which release their ingredients very quickly. *In vitro* testing may not always reflect the real *in vivo* disintegration of tablets.

In general, the method described in the US Pharmacopoeia can produce data for evaluation of the disintegration time; however, no additional information might be extracted.

It is also possible to evaluate the tendency of the disintegration kinetics by visual examination. However, these evaluations are not sufficiently objective. When developing FDT formulations, it is important to evaluate the effect of different excipients on the disintegration time. In order to predict the disintegration time of ODTs and the effects of different formulation parameters, a few methods have been proposed.[33]

It is important to define a suitable method to better distinguish between the disintegration times of different ODTs and to find better correlation between *in vitro* and *in vivo* data. To achieve this goal, a modified dissolution apparatus was applied to ODTs with disintegration times too fast to distinguish the differences between the tablets when the conventional methods were used.

**Texture analyzer method:**

The Texture Analyzer was applied to the beginning and ending time of disintegration. A tablet was adhered to the bottom of a probe, which was attached to the load cell with a very thin layer of glue or double-sided tape. A small amount of water, usually 0.4ml, in a beaker or petridish was used as a disintegration medium at room temperature.

The tablet was submerged in water and compressed against the bottom of the beaker or Petri dish with a constant pressure.

The beaker side could be varied and the beaker could even be a water bath to keep the temperature constant. The instrument was programmed to apply a moderate force for up to 60 seconds so that the penetration distance could be measured as the tablet was compressed while submerged in the water. The probe distance would be steady as the tablet remained cohesive. However, has the tablet disintegrated the compression distances increased, because the probe had to keep the pressure constant. The time for the tablet to disintegrate was determined by measuring the distance the probe traveled into the tablet. Topical time distance profiles generated by the texture analyzer software enabled the calculation of beginning and ending of disintegration time.[32]

**Sieve method:**

A simple device based on a shaking water bath is designed to measure the disintegration time of ODTs. The device is composed of a sieve (no.10) and a glass cylinder. The sieve is placed into the cylinder at a certain position so that 2ml of disintegration medium fills the space below the sieve of the cylinder.

Then 1ml of the medium is added into the device, so that it is available for an ODT to be tested. The device is in a reciprocal shaking water bath kept at a constant temperature of 37ºC. While the shaker is running in horizontal back-and-forth motions with 150 rpm, an ODT is placed onto the top of the sieve immersed in the disintegration medium. The ODT starts disintegration into small particles and/or dissolves, and the time at which particles of the tablet go through the sieve completely is determined as the disintegration time. The disintegration time is

measured using a stopwatch and this quick method gives reproducible data that are highly useful in screening various formulations and testing many formulations variables.[27]

**Dissolution:**

The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph; in a good place to start with scouting runs for a bioequivalent ODT.

USP Dissolution apparatus I and II can be used. USP I Basket apparatus may have certain applications but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles . The USP II Paddle apparatus, which is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. [33]

The USP II Paddle apparatus 50-100 rpm is suitable for dissolution testing of taste-masked drug as well. The media used for the taste-masked drug should match that of the finished product to maximize the value of the test. HPLC is often required to analyze dissolution aliquots due to presence of UV absorbing components, specifically flavors and sweetener. Excipient to drug ratio may be higher since the formulation is designed to have good taste and mouth feel, decreasing the detection of the drug to background (excipient) in the UV spectrophotometer.[36]

**1.5. Advantages and limitations of ODTs:**

The administration of ODTs may not inherently result in faster therapeutic onset, but can circumvent problems such as difficulty in swallowing traditional solid oral dosage forms such as tablets and capsules, particularly by pediatric and geriatric patients.

The driving force in developing an ODT or other quick dissolving intraoral dosage forms may include one or more of the following advantages.[28]

**Patient compliance***:* To allow patients to easily swallow the dosage form anytime, anywhere, for systemic absorption via rapid dissolution or disintegration in the oral cavity.

**Patient convenience**: To enhance convenience to the patients in carrying and administering these dosage forms especially when traveling by designing them to taken without water.

**Rapid absorption and onset of action***:*

To produce rapid absorption and faster onset of therapeutic efficacy mainly from the rapid disintegrating/ dissolvingdosage forms, presumably due to rapid disintegration, dissolution, and absorption.(i.e. antianginal therapy)[33]

**Avoidance of first-pass effect**:

To improve bioavailability owing to partial avoidance of first-pass metabolism resulting from at least partial absorption through the buccal mucosa.

**Elimination of water /improved stability**: To provide an alternative to liquid dosage forms (i.e., syrups, solutions, dispersions) and thereby improve physical/chemical stability of the drug.

In contrast to the advantages, many ODTs have limitations in terms or the amount of drug that can be incorporated in each unit dose. For lyophilized dosage forms, the drug dose must generally be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. Also due to the nature of ODTs, special packaging is needed for products that are fragile, which may add to the cost.[32]

**1.6. Packaging of ODTs:**

Packing is one of the important aspects in manufacturing ODT. The products obtained by various technologies vary in some of the parameters especially in mechanical strength to a good extent.

The products obtained by lyophilization process including various technologies such as Zydis, Lyoc, Quicksolv and Nanocrystal are porous in nature, have less physical resistance, sensitive to moisture and may degrade at higher humidity conditions.

For the above reasons products obtained require special packing. Zydis units are generally packed with peelable backing foil. Upon prototype selection, selection of a packaging configuration is a crucial part of an ODT dosage form. Unlike conventional tablets, where packaging provides a means of administration/transport, ODTs may require specialized packaging configurations owing to their relative high moisture sensitivity and fragility.

In fact, the cost of packaging can be significant for commercialization one approach used to overcome the moisture and physical issues with ODTs is to select a rigid, multilayer foil- based barrier material to protect the dosage form, with the blister actually forming during the tablet formulation process.

In many cases, ODT are very fragile and regular push through blister packaging may break the tablet upon removing from the blister, so the packaging requires a peelable closure. Packaging made from formable and flexible material can offer protection from water, oxygen or ultraviolet rays as well as providing some physical protection.[36]

The most common packaging configuration includes blister packaging and bottle packaging. Blister packaged ODTs require specialized packaging equipment. In case of CIMA's PakSolv technology, tablets are picked and placed in individual blister pockets ''one at a time'' using a robotic hand. In the case of freeze drying technology, each blister needs to be filled individually with the solution or suspension before subjecting it to freeze drying.

The final packaged dosage form has to be evaluated to verify packaging integrity. One way to perform this is by immersing blisters in water and subjecting them to a vacuum for a specified period of time. The blisters are then opened manually and checked for presence of water droplets. Additionally, blisters and bottles should be monitored in simulated shipping tests according to American Society for Testing Materials (ASTM) standards.

An additional issue with blister packaging is the evaluation of child resistance. The Consumer product safety commission regulates this. The blisters are evaluated for ''F '' value and appropriate designs need to be in place for child resistance and senior friendliness.

The F requirement is determined from the toxicity of the drug. In the case of tablets, this would be the number of tablets that when ingested may produce a serious injury or serious illness based on a 25-pound child. A package passes a certain F rating, if 90% of the children from an initial 50-child test are not successful in accessing the required F number of tablets.

Commercialization of ODTs has to go through the final evaluation of long-term stability of the tablet matrix and packaging components as per International Conference on Harmonization (ICH) guidelines. As the majority of ODT dosage forms on the market are sensitive to moisture, evaluation of moisture vapor transmission rate is an important parameter for assessing the shelf life of the product. Some ODTs are sensitive to moisture to such an extent that, even during processing or formulation development stages, temperature and humidity have to be controlled to avoid long-term stability issues and may require special packaging. Long-term stability studies done with several ODT products have indicated that the foil–foil blister Paksolv blister design leads to a mere 0.1% increase in moisture level compared to start over six months at 40ºC /75% RH. The increase in moisture level for high density polyethylene (HDPE) bottles is about 0.5% under the same stability conditions at the end of six months based on CIMA in-house experience on all bottled products.

Some of the products obtained from Durasolv, WOW tab, Pharmaburst, Oraquick, Ziplets, etc. technologies have sufficient mechanical strength to withstand transport and handling shock so they are generally packed in push through blisters or in bottles.

**1.7.Ideal characteristics of ODTs: Fast disintegration:**

ODTs should disintegrate in the mouth without additional water, the disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste of liquid suspension, which can provide good mouth feel and smooth swallowing.

The “fast disintegration” usually means disintegration of tablets in less than 1 min, but it is preferred to have disintegration as soon as possible.[5]

**Taste:**

As most drugs are unpalatable, ODTs usually contain the medicament in taste masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

**Drug properties:**

For the ideal ODT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of ODTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablets characteristics, such as tablet strength and disintegration. The ODT technology should be versatile enough to accommodate unique properties of each drug.[1]

**Tablet strength:**

Because ODTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability and the tablet structure should also have a highly porous network.

**Moisture sensitivity:**

ODTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect ODTs from various environmental conditions.[49]

**Friability:**

In order to allow oral disintegrating tablets to dissolve in the mouth, they are made of either very porous or soft moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packaging. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets.[50]

**Mouth feel:**

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the 'dryness' of a product.

**1.8. Taste masking:**

Success of ODT lies in its good taste. It does not matter if an ODT product disintegrates in just a few seconds if it does not taste good. Disintegration time variations of 5 to 30secs were considered to be fast by patients, and products in this range were acceptable if the product tasted good. If the product tasted bad, it didn't matter what the disintegration time was. So product does not tastes good, patients and physicians will find another ODT as so many pharmaceutical manufacturers are now switching to ODT technology and offering a wider choice of pharmaceutical actives covering many therapeutic categories to both physicians and Patients.

Moreover, consumers have become more knowledgeable and demanding due to many reasons including direct-to-consumer advertising, websites offering medical information and the increasing number of medicines available over the counter. Nowadays, consumers also have a greater power of choice than ever before.[8]

Taste is a sensation which is realized when a substance such as food, beverages or drug is placed in to the oral cavity. This sensation is the result of signal transudation from the receptor organs for taste, commonly known as taste buds.

These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste. More than 50 percent of pharmaceutical products are orally administered for several reasons; undesirable taste is one of the important formulation problems that are encountered with certain drugs.[9]

Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers, especially with pediatrics and geriatric patients. Thus, elimination or reduction of bitterness is an important main stay of product evaluation in oral pharmaceutical formulation. Proven methods for bitterness reduction have resulted in improved palatability of oral pharmaceutical formulations. Various techniques have been developed to improve taste like polymeric coating strategies, complexation with cyclodextrins, ion exchange resins, and salt formation using liposomes, microencapsulation technique and use of excipients like flavors, sweeteners and surfactants. [9]

**Table I: Flavors used in ODTs: [12]**

| Basic Taste | Recommended Flavor |
|---|---|
| Sweet | Vanilla, Bubblegum, Grape fruit |
| Salt | Butter scotch, maple, apricot, peach, vanilla, |
| Sour | Lemon, lime, orange, cherry, grapefruit |
| Bitter | Liquorices, coffee, chocolate, mint, grapefruit, cherry, peach, raspberry, orange, lemon, lime |

**Selection of drug:**

An ODT may have varying degrees of pre-gastric absorption and thus, the pharmacokinetic profile (including the maximum plasma concentration, time to achieve maximal plasma concentration, and area under the plasma concentration time curve of an equal dose of an ODT and a conventional oral dosage form) will vary. Therefore, the ODT will not be bioequivalent to the conventional oral dosage form.[51]

The ideal characteristics of a drug for dissolution in the mouth and pre-gastric absorption from an ODT include:

- No bitter taste,
- Dose lower than 20mg,
- Small to moderate molecular weight,
- Good solubility in water and saliva,
- Partially non-ionized at the oral cavity's pH,
- Ability to diffuse and partition into the epithelium of the upper GIT (log P>1, or preferably >2),

In contrast, the following characteristics may render a drug unsuitable for delivery as an ODT.

- Short half-life and frequent dosing;
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved;
- Require controlled or sustained release.

**1.9. Superdisintegrants:**

Addition of disintegrants in ODTs, leads to quick disintegration of tablets and hence improves dissolution. In many ODT technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. Tablet disintegration time can be optimized by

concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increase.[33]

Microcrystalline cellulose, cross linked carboxy methyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, though water insoluble, absorb water and swell due to capillary action.

Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug.

The major drawback of effervescent excipients is their hygroscopicity (i.e., the ability to absorb atmospheric moisture). Hence, their manufacture requires control of humidity conditions and protection of the final product. This is reflected by overall cost of the product.[54]

**Method of addition:**

Disintegrants are substances or mixture of substances added to the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-15% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are croscarmellose sodium, crospovidone, sodium starch glycolate which represent examples of a cross linked cellulose, cross linked polymer and a cross linked starch respectively.

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment.

There are three methods of incorporating disintegrating agents into the tablet:

- Internal addition (Intra granular)
- External addition (Extra granular)
- Partly internal and external

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrant is mixed with other powders before wetting the power mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used, part of disintegrant can be added internally and part externally.

This provides immediate disruption of the tablet into previously compressed granules while that disintegrating agent within the granules produces further erosion of the granules to the original powder particles. The two step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.[54]

**Mechanism of action:**

Disintegrant is a substance or mixture of substances added to tablets to facilitate its break up or disintegration. The active constituents must be released from the tablet as efficiently as possible to allow its rapid action. The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension is based on:

- Capillary action
- High swellability
- Capillary action and high swellability
- Deformation

**By capillary action:**

Here the medium penetrates into the tablet and replaces the air adsorbed on the particulars, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of drug/excipient and on tabletting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegrations by creating a hydrophilic network around the drug particles.

**By swelling action:**

Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart their disintegrating effect.

By swelling in contact with water, the adhesiveness of other ingredients in a tablet overcomes causing the tablet to fall apart.

**Deformation:**

Starch grains are generally thought to be "elastic" in nature meaning that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved with tabletting, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water.

In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure.[53]

It is believed that no single mechanism is responsible for the action of most disintegrants. But rather; it is more likely the result of inter-relationships between these major mechanisms.

**Table 2: Superdisintegrants and their properties**[57]

| Superdisintegrant | Nature | Properties | Mechanism |
|---|---|---|---|
| Crospovidone | Cross-linked homo polymer of N-vinyl-2-Pyrrolidone | Particle size- 100 microns. | Both swelling and wicking. |
| Croscarmellose Sodium | Cross-linked form of Sodium CMC (Carboxy methyl cellulose) | Insoluble in water. Gives smoother mouth feel. Particle size -200 microns. | Swelling. |
| Sodium Starch Glycolate | Cross-linked low substituted carboxy methyl ether of poly-glucopyranose | Insoluble in water. Particle size -140 microns. | Water uptake followed by rapid and enormous swelling. |

**Need for the study:**

Asthma is a chronic inflammatory disease, which includes bronchial hyperactivity and bronchospasm characterized by hyper responsiveness of trachea bronchial smooth muscle to variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretions and mucosal edema resulting in breathlessness or dyspnea, wheezing cough and chest congestion.

Asthma affects over 5-10% of population in industrialized countries. It afflicts approximately

53 million people across world mostly in United States, France, Germany, Italy, Spain, United Kingdom and Japan.[50] The treatment of asthmatic symptoms generally includes conventional oral dosage forms like tablets, capsules, oral liquids etc.; inhalation therapy includes metered dose inhalers with or without spacers, dry powder inhalers and other aerosol systems.

Oral administration is the most widely accepted route of delivery due to its ease of administration, convenience, versatility and most importantly patient compliance. Several new technologies for oral delivery have recently been available to address the problems of physicochemical and pharmacokinetic characteristic of drugs, while improving patient compliance.

One of these include fast dissolving technology which offers the advantages of both solids and liquids such as quick disintegration and dissolution of tablets, no residue in mouth, requires no water intake, provides a pleasant mouth feel.[51]An attempt was made for preparation of fast dissolving tablets of a model bronchodilator, Salbutamol sulphate with an aim of reducing the lag time and providing faster onset of action to relieve immediately acute asthmatic attack. This would be advantageous as conventional solid oral dosage forms are often associated with a longer lag time and thus slower onset of action, while oral liquids prove to have faster onset of action but require careful handling. Aerosol systems are specific but fail to deliver the actual dose of drug with only ten percent of administered dose deposited on the bronchi while rest of the drug is deposited in oro-pharynx and is swallowed.

Also, metered dose systems are less potable while dry powder inhalers cause clogging of device and require skillful operation. A fast dissolving tablet form would thus be advantageous, as Salbutamol sulphate is water-soluble and its preparation into a fast dissolving form would render it to dissolve rapidly and thereby result in rapid absorption.[51]

The concept of mouth dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence, they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy.

In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Such problems can be resolved by means of mouth dissolving tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water. The faster the drug disintegrates in to solution, the quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.[51]

Hence, in the present study an attempt will be made to formulate mouth dissolving tablets of salbutamol sulphate (a direct-acting sympathomimetic with predominantly β-adrenergic activity and a selective action on β2 receptor (β2agonist), used as bronchodilators in the management of reversible obstruction as in asthma, with a view to develop a convenient means of administration to those patients suffering from difficulties in swallowing, nausea and motion sickness.

**Past Work On Mouth Dissolving Tablets**:

- **Popa G *et al.*, 2000[53]** optimized orodispersible tablets of Meloxicam. The tablets were made by non –aqueous wet granulation using crospovidone and mannitol. A $2^2$ factorial design was used to investigate the amount of crospovidone and taste masking, smoothening hydrophilic agents (mannitol), as independent variables and disintegration time as dependent response. The results show that the presence of a super disintegrant and mannitol is desirable for orodispersion.

- **Prabu *et al.*, 2010[54]** prepared disintegrating tablets of taste masking drug. Taste masking was done by complexing Ondansetron HCL with amino alkyl methacrylate copolymer in different ratios by precipitation method. Taste evaluation of Rapidly Disintegrating Tablet in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value ultimately reaching to within 15mins.

- **Reddy *et al.*, 2002[55]** prepared rapidly disintegrating tablets of Chlorpheniramine maleate, a bitter drug. The taste masked granules were prepared using amino alkyl methacrylate copolymer by the extrusion method. The taste masked granules were directly compressed into tablets using Sodium Starch Glycolate as super-disintegrant. Tablets having good taste and disintegrated in the oral cavity is within 30secs.

- **Redkar *et al.*, 2002[56]** attempted to mask the taste and to formulate an oro- dispersible tablet of Ambroxyl Hydrochloride by complexation. Ion exchange resin unlike Indion-204 and Indion-234 were utilized for the sorption of drug. Prepared tablets were evaluated and both the resins have shown quick disintegration features (within 20secs), which is an important characteristic of oro-dispersible tablets.

- **Reeta *et al.*, 2011[57]** studied the formulation of fast dissolving tablets of poorly soluble Carbamazepine by the direct compression technique with β-cyclodextrin complexes using super disintegrants, like Indion-414, croscarmellose sodium, crospovidone and Sodium Starch Glycolate. To enhance the solubility of the drug, a complex of carbamazepine was prepared with β-cyclodextrin and this complex was compressed into tablets.

The stability study was conducted as per the ICH guidelines and the formulations were found to be stable, with insignificant changes in hardness, drug content and disintegration time.

- **S Schiermeir *et al.*, 2002**[58] evaluated the fast dissolving tablet of Terbutalin sulfate by the direct compression method after incorporation of super-disintegrants such as Explotab, Ac-di-sol and polyplasdone XL in different concentration. An increase in dissolution rate was observed.

- **Sarasija *et al.*, 2007**[59] prepared and evaluated orodispersible tablets of Ondansetron Hcl using a direct compression method with combination of glycein and chitosan used as disintegrating substance.

- **Seager *et al.*, 1990**[60] developed Ondansetron Hydrochloride mouth dissolving tablet which can disintegrate rapidly once placed in the oral cavity. Treated agar powder was used along with regular superdisintegrants (AC-Di-Sol, Polyplasdone XL, Explotab) to check its disintegrating property.

- **Seager *et al.*, 1998**[61] prepared Ondansetron Hydrochloride tablet by direct Compression using sodium starch glycolate and croscarmellose sodium as superdisintegrants. The results of *in vitro* disintegration time and *in vivo* disintegration time indicated that the tablets dispersed rapidly in mouth within 3 to 5 secs. Addition of superdisintegrants is a useful method for preparing orodispersible tablets by direct compression method.

- **Sreenivas *et al.*,2006**[62] prepared a fast dissolving tablet of Domperidone using Avicel pH 102 and sodium starch glycolate by direct compression method. An effective pleasant tasting formulation was found to have a good hardness, disintegration time and *in vitro* drug release of not less than 95% within 30 mins. The drug release was found to be increased when compared with the marketed available dispersible tablet.

- **Subranmyam *et al.*, 2007**[63] prepared fast water dispersible tablet containing Domperidone for oral administration. The formulation has an enhanced structural integrity, for instance having friability lower than 1.0% and hardness value between 3 and 6 kg/cm$^2$ and having a pleasant taste.

- **Sunada *et al.*, 2002**[64] developed rapid oral disintegration tablets by direct compression using co-ground mixture prepared with a vibration rod mill. The tablets were formed by compression using a single punch- tabletting machine after addition of the co- ground mixture to non-ground D-Mannitol, Crospovidone and Magnesium Stearate. Hence, in this crospovidone acted as a grinding assistant for D-Mannitol in the co- grinding process, enhancing the hardness of the tablet by increasing the contact area among powder particles.

- **Suryakanta *et al., 2010***[65] prepared rapidly disintegrating tablet using microcrystalline cellulose (Avicel PH-M series), a new type of pharmaceutical excipient that is spherical and has a very small particle size instead of conventional microcrystalline cellulose used in formulation of the tablets. To decrease the sense of roughness, rapidly disintegrating tablets can be prepared by direct compression method when suitable excipients such as fine microcrystalline cellulose (PH-M-06) and spherical sugar granules are used.

- **T. Hanawa *et al.*, 1995**[66] evaluated the effects of the oral Ondansetron disintegration tablet on the incidence of the emesis in children undergoing tonsillectomy with and without adenoidectomy and with and without bilateral myringotomy and tube insertion. Randomized patients were selected and they were followed for the first 3 days after surgery. At home use of oral disintegrating tablet may prevent emesis in children during the first 3 days after tonsillectomy in children.

- **Tripati *et al.*, 2008**[67] formulated and developed taste- masked rapid disintegrating formulations of Cetirizine hydrochloride using various grades of HPMC (Hydroxy Propyl Methyl Cellulose) for patients, who experience difficulty in swallowing the tablet. Taste masking could be achieved using suitable sweeteners, flavors and sour ingredients.

- **Wilkosz *et al., 2003***[68] produced a novel, a taste masked, fast disintegrating tablet of Famotidine. The disintegration time was improved considerably by controlling ambient humidity during the compression process. A new fast-disintegrating technology made it possible to use low compression force, there was no change in structure or dissolution rate of the taste- masked particles after compression.

- **Y Morita *et al., 2002*[69]** reported the formulation of mouth dissolving tablets of Roxithromycin, Dicyclomine HCl and Montelukast sodium using Indion 414 as super disintegrant. It was found, that Indion 414 exhibited very good superdisintegrant action resulting in cost effective formulation and that their use can be extended to various other fast disintegrating dosage forms

- **Yunxia *et al., 1996*[70]** evaluated rapidly disintegrating tablets prepared by a direct compression method using excipients like microcrystalline cellulose, lactose croscarmellose sodium and erythritol. Within the optimal region the minimum tensile strength was 5 $kg/cm^2$, while the maximum disintegration time was 15 secs. The method described here was useful for the preparation of rapidly disintegrating tablets.

- **A. Watanabe *et al.*, 1994**[71] developed orodispersible tablets of Ondansetron Hcl by Direct compression technique using various superdisintegrants, such as SSG, croscarmellose, individually and in combination. Results have shown that orodispersible tablets have a greater drug release than marketed conventional tablet formulations.

- **AC Liang *et al.,2001***[72] developed Metformin Hcl fast disintegrating tablets by using polacrillin potassium NF from different sources and superdisintegrants such as indion 294, tulshion 349, doshion, ambrilite. The results reveal that the tablets containing disintegrants had a good dissolution profile.

- **Akihiko *et al.,*** 1996[73] developed Metformin Hcl orodispersible tablets using natural disintegrants isphagula husk and synthetic disintegrants crospovidone. Results have shown that tablets prepared with isphagula husk have a greater dissolution rate.

- **Ansel *et al.1995,***[74] prepared orodispersible tablets of Baclofen using various concentrations of superdisintegrants like Ac-di-sol, crospovidone, sodium starch glycolate by direct compression method. Results revealed that disintegrant concentration affects the dissolution rate of the drug and superdisintegrants addition technique is a useful for preparing Orodispersible tablets by direct compression technique.

## AIM AND OBJECTIVE OF THE STUDY

- To prepare and evaluate Oro dispersible tablets of salbutamol sulphate using different super disintegrants in various concentrations by the process of wet granulation
- To do *in vitro* drug release studies using USP type II dissolution apparatus.
- To optimize the formula having the greatest bioavailability.
- To prepare and evaluate ODTs of the optimized formulation by changing the manufacturing methods to direct compression and sublimation.
- To compare the drug release profile of the orodispersible tablet with that of a marketed conventional tablet.

# PLAN OF WORK

- Selection of drug and excipients.
- Preparation of standard graph of the drug in suitable media.
- Solubility studies of salbutamol sulphate in various media.
- Preformulation studies: Drug -excipient compatibility, powder properties
- Preparation of oro dispersible tablets of salbutamol sulphate by wet granulation method using different concentrations of superdisintegrants.
- Evaluation of the prepared tablets and optimizing the formulation having a better release profile.
- Preparation of ODTs of the optimized formulation by changing the manufacturing methods to direct compression and sublimation and then evaluating them to optimize the best method.
- Comparing the best formulation with a marketed conventional tablet of salbutamol sulphate.

**5.1. Drug profile of Salbutamol sulphate**

**Chemical Names:**

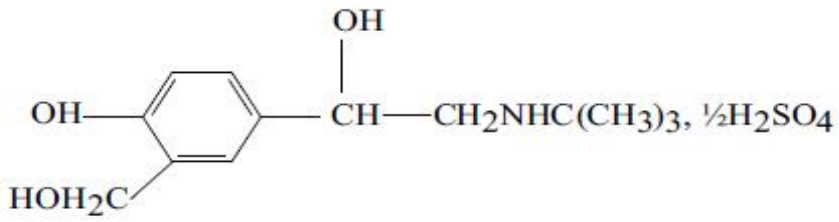
a) 1, 3-benzene dimethanol α′{[(1,1-dimethyl ethyl) amino] methyl}-4-hydroxysulphate (2:1) salt.

b) M-xylene-α-α′ diol α′ [(tert butyl amino) methyl] 4-hydroxy α′ [(tertbutylamino) methyl]-4 hydroxy m-xylene α, α′-diol.

c) α (tertbutylamino)-1-(4-hydroxy 3 hydroxy methyl phenyl) ethanol.

d) 4-hydroxy-3-hydroxy-methyl α [(terbutylamino) methyl] benzyl alcohol. e) 1-(4-hydroxy-3 hydroxy methyl phenyl)-2 (terbutylamino) ethanol

**Structural Formula:**




**Molecular weight**: 288.35

**Description**: White or almost white powder, odorless and slightly bitter in taste.

**Standards**: Salbutamol sulphate IP (1985) contains not less than 98% and not more than 102% salbutamol calculated with reference to the dried substance.

**Solubility**: Soluble one in four parts of water. Slightly soluble in ethanol, 96% chloroform and ether.

**Storage**: It should be protected from light.

**Melting point**: 150ºC.

**Synonym**: Albuterol sulphate.

**Category**: This drug is a selectively acting beta-2-receptor stimulant (agonist) essentially devoid of α and β activity. It is a direct acting adrenergic, sympathomimetic bronchodilator.

**Pharmacokinetic properties: Absorption**:

Rapidly absorbed after oral administration and after inhalation; most of the inhaled dose is swallowed and more enters the lungs with positive intermittent breathing than by aerosol.

**Distribution**:

After an oral dose of 4-8mg, peak plasma concentration of about 23ng/ml for unchanged drug and 50-100ng/ml for drug plus metabolite are attained in 2.5-3hrs. After an inhaled dose of 80 μg, peak plasma concentrations of about 0.2ng/ml for unchanged drug and about 1ng/ml for drug plus metabolite are attained in about 3hrs; 2hrs after an intravenous dose of 200μg plasma concentration of about 1ng/ml is obtained for the unchanged drug and about 2ng/ml for drug plus metabolite.

**Metabolism**:

The drug is metabolized by the first pass metabolism, the reactions and metabolites involved are not yet identified.

**Elimination**:

About 75-95% of an oral dose is excreted in urine and about 4% in the feces in 3 days, after administration as an aerosol, up to 97% is excreted in the urine and about 11% in the feces, after IV dose 80% is excreted in the urine and 4% in feces, about 20% of an inhaled dose is lost in the air and in the oral adapter following oral administration or inhalation. About 50- 60% of the urinary excreted material is metabolized but after intravenous administration only about 27% is excreted in metabolized form. The inactive metabolite is sulphate conjugate and about 25% of the administered dose is metabolized to the sulphate ester.

**Half-Life**:

Plasma half-life is 2-7hrs. In general, the shorter half-life is seen with intravenous administration, the intermediate values after oral administration and the

longer values after aerosol inhalation. It has been suggested that the slightly extended half-life following inhalation may be due to slow removal of active drug from the lungs. Salbutamol does not cross the blood brain barrier to a significant extent, but it crosses the placental barrier

**Pharmacology:**

Salbutamol exerts a relatively selective action on the β2 adrenergic receptors of the bronchial and vascular smooth muscles. It is administered either by inhalation or orally for the symptomatic relief of bronchospasm associated with chronic or acute asthma, bronchitis or other obstructive pulmonary diseases.

**Action:**

Salbutamol is a directly acting sympathomimetic amine with a more selective action than isoprenaline. Albuterol is long lasting and less likely to cause cardiovascular side effects than other adrenergic bronchodilators. It may be a preferred adrenergic agonist because it produces minimal arrhythmia and fall in the partial pressure of peripheral arteriolar oxygen. It causes slight fall in blood pressure rather than an increase.

**Uses:**

It is used in the treatment of asthma, chronic bronchitis, emphysema and other broncho- pulmonary disorders involving bronchospasm. The drug is also used to arrest premature labor and in ocular hypertension. In congestive heart disease, it is used for low output states. The drug improves cardiac output by reducing left ventricular after load but has little effect on ventricular filling pressure.

**Dose:**

Salbutamol is used as the base in aerosol inhalers and as the sulphate salt in other dosage forms. A dose equivalent to 2 to 4mg of salbutamol, 3 or 4 times per day is prescribed for adults, while for children of 2-6years, a dose of 1-2mg, 3 or 4 times and 2mg for older children is prescribed.

Salbutamol is administered as an aerosol inhalation in doses of up to 200µg 3 or 4 times a day. The usual dose for children is on inhalation of 100µg 2-4 times daily. Salbutamol sulphate is used as a respiratory solution containing the

equivalent of 0.5% salbutamol. A solution for injection containing the equivalent of 50 or 500µg or one mg of salbutamol per ml is used in bronchospasm.

The usual dose by subcutaneous or intramuscular injection is equivalent of 8µg of salbutamol per kg body weight every 4 hours and slow intravenous injection, 4µg/Kg body weight, repeated as necessary.

Note: 1.2mg of salbutamol sulphate is approximately equivalent to 1mg of salbutamol.

**Adverse effects:**

Salbutamol sulphate may give rise to tremor of skeletal muscle (fine finger tremor), palpitations and muscle cramps, slight tachycardia, tenseness, headaches and peripheral vasodilation after longer doses. The injection may give rise to nausea, vomiting and headache. This can be treated by using a cardioselective β-adrenoreceptor blocking agent.

**Precautions and contraindications:**

It is contraindicated in patients with hypertension, myocardial insufficiency and hyperthyroidism and in patients with diabetes mellitus, serious cardiovascular disorders. The excessive use of spray may lead to fatal results. It should not be administered with non- selective beta adrenoreceptor blocking drugs such as propranolol or oxprenolol.

**Tolerance:**

In healthy subjects specific airway conductance was progressively decreased when Salbutamol up to 400µg 4 times daily was inhaled over a period of 40 weeks. Hydrocortisone 200mg IV or aminophylline will restore the response.

**5.2. Excipient profile Croscarmellose sodium Synonyms**:

Ac-Di-Sol, cross-linked carboxy methyl cellulose sodium, modified cellulose gum, Nymcel, Primellose, Solutab.

**Functional Category**:

Tablet and Capsule disintegrant.

**Applications**:

As a disintegrant for tablets (wet granulation and direct compression), capsules and granules in 2-5 % concentration.

**Description**:

Odorless, white colored powder.

**Solubility**:

Insoluble in water, although it swells to 4 to 8 times its original volume on contact with water.

**Stability**:

It is a stable though hygroscopic material.

**Storage conditions**:

It should be stored in a well-closed container in a cool and dry place.

**Incompatibilities**:

Efficacy may be slightly reduced in formulations containing hygroscopic excipients like sorbitol.

**Safety**:

It is generally regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may have a laxative effect.

**Crospovidone**

**Synonyms**:

Cross-linked povidone, Polyplasdone XL, (PVPP) poly vinyl poly pyrrolidone.

**Functional Category**: Tablet disintegrant.

**Applications**:

This is a water insoluble tablet disintegrant used at 2-5 % concentration, in tablets prepared by direct compression or wet and dry granulation method.

**Description**:

White to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless and hygroscopic powder.

**Solubility**:

Practically insoluble in water and most organic solvents.

**Stability**:

Crospovidone is stable.

**Storage conditions**:

Since it is hygroscopic it should be stored in an airtight container in a cool and dry place.

**Incompatibilities**:

When exposed to a high water level it may form molecular adducts with some materials.

**Safety**:

It is generally regarded as a non-toxic and non-irritant material.

**Sodium starch glycolate**

**Synonyms**:

Carboxymethyl starch, Explotab, Primogel.

**Functional Category**:

Tablet and capsule disintegrant.

**Applications**:

As a disintegrant in tablet (wet granulation and direct compression) and capsule formulations in 2-8 % concentration.

**Description**:

White to off-white, odorless, tasteless, free-flowing powder.

**Solubility**:

Practically insoluble in water, sparingly soluble in ethanol (95 %). In water it swells up to 300 times to its volume.

**Stability**: It is a stable material.

**Storage conditions**:

It should be stored in a well-closed container to protect from wide variations in humidity and temperature that may cause cracking.

**Incompatibilities**:

Incompatible with ascorbic acid.

**Safety**:

It is generally regarded as a non-toxic and non-irritant material.

**Microcrystalline cellulose**

**Synonyms**:

Avicel, cellulose gel, crystalline cellulose, E460, Emocel, Fibrocel,Tabulose, Vivacel.

**Functional Category**:

Tablet and capsule diluent, suspending agent, adsorbent and tablet disintegrant

**Applications**:

As a diluent in tablets (wet granulation and direct compression) and capsule formulations. In addition to its use as a diluent, it also has some lubricant and disintegrant property.

**Description**:

White-colored, odorless, tasteless crystalline powder composed of porous particles. Available in different particle size grades which have different properties and applications.

**Solubility**:

Slightly soluble in 5 % w/v sodium hydroxide solution, practically insoluble in

water, dilute acids and most organic solvents.

**Stability**:

It is a stable, though hygroscopic material.

**Storage conditions**:

The bulk material should be stored in a well-closed container in a cool and dry place.

**Incompatibilities**:

Incompatible with strong oxidizing agents.

**Safety:**

It is generally regarded as a non-toxic and non-irritant material.

**Description**:

White-colored, odorless, tasteless crystalline powder composed of porous particles. Available in different particle size grades which have different properties and applications.

**Solubility**:

Slightly soluble in 5 % w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.

**Stability**:

It is a stable, though hygroscopic material.

**Storage conditions**:

The bulk material should be stored in a well-closed container in a cool and dry place.

**Incompatibilities**:

Incompatible with strong oxidizing agents.

**Safety:**

It is generally regarded as a non-toxic and non-irritant material.

**Table 3: List of materials used and manufacturer**

| S.NO. | MATERIALS | MANUFACTURER |
|---|---|---|
| 1 | Drug (Salbutamol sulphate) | Cipla ,India |
| 2 | Diluent (Avicel) | SK Pharm ltd.,hyd SK |
| 3 | Superdisintegrants (Polyplasdone, Explotab, ac-di-sol) | Pharm ltd.,hyd SK |
| 4 | Glidant (Aerosil) | Pharm ltd.,hyd SK |
| 5 | Lubricant(Magnesium fumarate) | Pharm ltd.,hyd krishna |
| 6 | Flavor (mango ) | Pharm.,hyd |

**Table 4: List of equipments used**

| S.NO | EQUIPMENT | MANUFACTURER |
|---|---|---|
| 1 | UV-Vis spectrophotometer | Elico corporation instruments (SL 162) |
| 2 | Rotary tablet punching machine | Rimek, Ahmedabad. |
| 3 | Dissolution apparatus | Electro lab TDT- 08L, Mumbai. |
| 4 | Friabilator | SECOA, New Delhi. |
| 5 | Hardness tester | Monsanto hardness tester, Hyd. |
| 6 | Electronic balance | AW 120, Shimadzu Corporation, Japan. |

**6.1. Evaluation of pre-compression blend**

**1. Angle of repose:**

The prepared granules were assessed for the flow property by determining the angle of repose. The angle of repose was measured by allowing the granules to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height (about 6 cm). The height of the heap (h) was measured and then circumference of the base of heap (r) was drawn on graph sheet with the help of a pencil. The radius of the circle obtained was measured. The angle of repose was calculated by the following equation.

$\tan \theta = h/r$ or $\theta = \tan^{-1} (h/r)$

Where $\theta$ = angle of repose

h = height of the heap

r = radius of the base of the heap.

**Table 5: Angle of repose as an indication of powder flow properties**

| FLOW PROPERTIES | ANGLE OF REPOSE ($^{O}$) |
|---|---|
| Excellent | 25-30 |
| Good | 31-35 |
| Fair | 36-40 |
| Passable | 41-45 |
| Poor | 46-55 |
| Very poor | 56-65 |

**2. Bulk density:**

It is the ratio of total mass of granules to the bulk volume of granules. It was measured by pouring the weighed granules into a measuring cylinder and initial volume was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned.

It is expressed in gm/ml and is given by,

$$\rho b = \frac{M\ V}{VB}$$

Where, M = mass of granules

Vb = bulk volume

**3. Tapped density:**

After determining the poured bulk density, the measuring cylinder containing known mass of powder was tapped mechanically for fixed time to attain constant volume, called tapped density.

$$\text{Tapped density} = \frac{\text{Mass of granules}}{\text{Tapped volume of granules}}$$

4. **Carr's index (percentage compressibility):**

Using bulk density and tapped density the percentage compressibility of powder blend was determined, which is given as Carr's compressibility index.

$$\text{Carr's compressibility index (\%)} = \frac{\text{Tapped density- Bulk density} \times 100}{\text{Tapped density}}$$

**Table 6: Percentage compressibility and flowability of powder**

| PERCENTAGE COMPRESSIBILITY | FLOWABILITY |
|---|---|
| 5 – 12 | Excellent |
| 12 – 16 | Good |
| 18 – 21 | Fair Passable |
| 23 – 35 | Poor |
| 33 – 38 | Very Poor |
| < 40 | Very Very Poor |

**5. Hausner's ratio**:

It is determined by the ratio of tapped density and bulk density. Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's Ratio = $V_t / V_b$

Where,

$V_t$ = tapped density

$V_b$ = bulk density

**Table 7: Table showing flow character and Hausner's ratio**

| FLOW CHARACTER | HAUSNER'S RATIO |
|---|---|
| Excellent | 1.00 – 1.11 |
| Good | 1.12 – 1.18 |
| Fair | 1.19 – 1.25 |
| Passable | 1.26 – 1.34 |
| Poor | 1.35 – 1.45 |
| Very Poor | 1.46 – 1.59 |

**6.2. Drug excipient compatibility**

**Physical observation (stability):**

The drug was mixed with different proportions of the excipients which were used in the formulation, in different ratios and kept at varying temperatures for a period of one month. The physical properties (color change) were monitored regularly. The change in color of any mixture was considered as incompatibility.

**FT-IR studies:**

The drug, physical mixture and the powdered tablet were subjected to IR studies to observe for any incompatibility between the drug and excipients.

**6.3. Solubility studies of Salbutamol sulphate:**

10 mg of the drug was dissolved in 100 ml of each of the solvent (water, phosphate buffer and ethanol) separately and mixed well. Absorbance of the resultant solution (5ml sample) was measured using U.V Visible spectrophotometer against distilled water as blank at a wave length of 275nm. Concentrations were calculated with the help of standard graph and total amount of drug solubilized in 1ml of the solvent was obtained.

**Table 8: Solubility terms**

| Solubility term | Parts of solvent required for 1 part of solute |
|---|---|
| Very soluble | Less than 1 part |
| Freely soluble | 1-10 parts |
| Soluble | 10-30 parts |
| Sparingly soluble | 30-100 parts |
| Slightly soluble | 100-1000 parts |
| Very slightly soluble | 1000-10,000 parts |
| Practically insoluble | >10,000 parts |

**6.4. Standard graph of Salbutamol sulphate in phosphate buffer of pH 6.8:**

A standard graph of pure drug in suitable medium was prepared by plotting the concentrations on X-axis and absorbance / optical density on Y-axis.

**Procedure:**

Accurately weighed amount of 100 mg of Salbutamol sulphate was taken in a 100 ml volumetric flask. The volume was made up to 100 ml with 6.8 pH phosphate buffer, which constitutes the stock solution of 1 mg/ml. By further diluting the stock solution suitably with fresh buffer, solutions of 1, 3, 5, 7, 10 and 15µg/ml concentrations were prepared. These solutions were checked for their absorbance using UV-Vis Spectrophotometer at $\lambda_{max}$ 275 nm against distilled water as blank and a standard graph was plotted.

**6.5. Manufacturing methods used:**

a) Wet granulation
b) Direct compression c) Sublimation

**a) Wet granulation:**

The steps followed in the formulation of ODTs by wet granulation technique includes weighing, mixing, moistening, wet screening, drying, dry screening, addition of lubricant and glidant and compressing.

**Procedure:**

All the required ingredients were weighed. Whole amount of drug, diluent, half of the amount of disintegrant were taken and wet mass was prepared with water. This wet mass is passed through sieve no. 10 to form the granules.

The granules were dried, these are again screened. To this mixture the remaining disintegrant, lubricant, and glidant and flavor were added. The final mixture was shaken manually for

10mins in a plastic bag. Final blend was compressed into tablets using 7mm round, flat punches at corresponding dies on rotary compression machine.

**b) Direct compression:**

All the required ingredients were passed through sieve no.10 to get uniform sized particles and were weighed accurately. Whole amount of drug, superdisintegrant, diluents and flavor were mixed in the increasing order of their weights in a polythene bag. To this mixture the glidant and lubricant were added .The final mixture was shaken manually for 10 mins in a plastic bag. Final blend was compressed into tablets using 7mm round, flat punches at corresponding dies on a rotary compression machine.

The process is similar for all the formulations, which were prepared by direct compression technique.

**Sublimation:**

Here, an additional ingredient - subliming agent (e.g. camphor) was added to the mixture and directly compressed. The resulting tablets were dried to volatilize any residues of camphor.

**6.6. Evaluation of the prepared tablets**

Different quality control tests were performed for all the ODT formulations to check whether these have met the specifications given in USP along with other *in vitro* tests like wetting time and water absorption ratio.

**Various *in vitro* tests performed are:**

- ✓ Weight variation
- ✓ Hardness and Friability
- ✓ Assay
- ✓ Wetting time and Water absorption ratio
- ✓ Disintegration Time
- ✓ Dissolution

**Weight variation test:**

20 tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight.

**Table 9: Limits for uniformity of weight**

| Average weight of tablets (mg) | Maximum percentage difference allowed |
|---|---|
| 130 or less | 10 |
| 130-324 | 7.5 |
| More than 324 | 5 |

**Hardness:**

The tablet hardness of different formulations was measured using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two

plungers. The lower plunger was placed in contact with the tablet and a zero was taken.

The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded and the zero force reading is deducted from it. Generally, a minimum hardness of 4 kg is considered acceptable for uncoated tablets. The hardness for ODTs should be preferably 1-3 kg.

**Friability (F):**

This test is performed using a laboratory friability tester known as Roche Friabilator. 10 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution.

The tablets were subjected to 100 revolutions for 4 mins. After the process, these tablets were de- dusted and reweighed. Percentage loss of tablet weight was calculated using the formula-

$$F = 100 \left[1 - \frac{Wo}{W}\right]$$

Where $w_0$ = initial weight

W=final weight

**Assay of the Tablets:**

The formulated orally disintegrating tablets were assayed for the drug content. In each formulation, samples containing amount of powder equivalent to one dose of drug were taken in triplicate and assayed for content of drug

**Method:**

10 tablets were randomly selected, weighed and finely powdered; powder equivalent to one tablet was added to 100ml of distilled water in a conical flask. The conical flask was placed on a rotary shaker overnight. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22µ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible spectrophotometer against distilled water as blank at a wave length of
275nm.

Concentrations were calculated with the help of standard graph and total amount present in the formulation was calculated.

**Wetting time and Water absorption ratio (R):**

Five circular tissue papers were placed in a petridish with a 10-cm diameter. Ten milliliters of water containing methylene blue, a water-soluble dye, was added to the petridish. The dye solution is used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicates (n=6). The wetting time was recorded using a stopwatch.

The weight of the tablet before keeping in the petridish was noted ($W_b$) using digital balance. The wetted tablet from the petridish was taken and reweighed ($W_a$) using the same. The water absorption ratio, R, was determined according to the following equation:

$R = 100 (Wa - W_b) / W_b$

Where $W_b$ and $W_a$ are the weight before and after water absorption respectively.

**Disintegration Time:**

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time *in vitro* and *in vivo* (in oral cavity) several methods were proposed, developed and followed at their convenience. One of the simple methods followed is described below.

Disintegration time was measured using a modified disintegration method (n=6). For this purpose, a petridish (10cm diameter) was filled with 10ml of water. The tablet was carefully put in the center of the petridish and the time for the tablet to completely disintegrate into fine
particles was noted using a stop watch.

**Dissolution test:**

Drug release from ODTs was studied by using dissolution rate test apparatus. ODTs of desired formulation were taken and placed in the vessels of dissolution apparatus.

5ml aliquots were collected from the vessels at different time intervals, replenished with same volume of the blank solution and analyzed by using UV Visible spectrophotometer at 275nm. Drug concentration was calculated from the standard graph and expressed as percentage of drug dissolved or released. The release studies were performed in 3 replicates and mean values were taken.

**Conditions for Salbutamol sulphate:**

| | | |
|---|---|---|
| Apparatus | : | Dissolution test apparatus (USP II) |
| Medium | : | 500 ml, phosphate buffer of pH 6.8 |
| RPM | : | 50 |
| Temperature | : | $37 \pm 0.5\ ^{0}$ C Sampling |
| Volume | : | 5ml |
| Sampling intervals | : | 3, 6, 9, 12, 15, 18, 21, 24, 27 and 30mins. |

**Table 10: Standard graph of Salbutamol sulphate in pH 6.8 phosphate buffer**

| Concentration (µg/ml) | Absorbance |
|---|---|
| 1 | 0.078 |
| 3 | 0.19 |
| 5 | 0.355 |
| 7 | 0.49 |
| 10 | 0.69 |
| 15 | 0.87 |

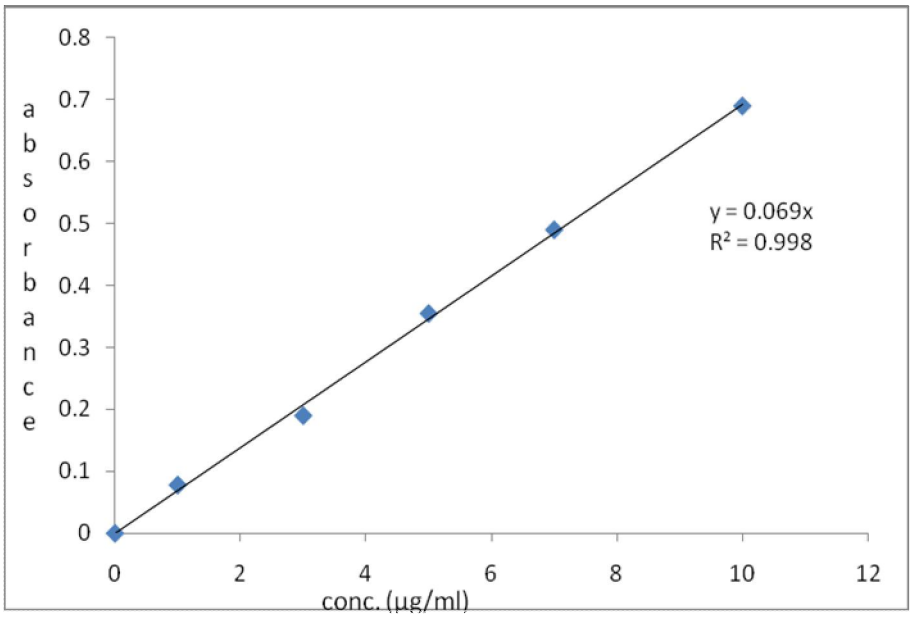



**Fig 1: Standard graph of Salbutamol sulphate in pH 6.8 phosphate buffer (at 275nm)**

**Table 11: Solubility studies of Salbutamol sulphate**

| Solvent | Solubility |
|---|---|
| Water | 0.95 mg/ml (freely soluble) |
| 6.8 pH phosphate buffer | 0.94 mg/ml (freely soluble) |
| Ethanol | 0.014 mg/ml (slightly soluble) |

Salbutamol sulphate was found to be freely soluble (1-10 parts of solvent required for 1 part of solute) in water and phosphate buffer of pH 6.8, slightly soluble (100-1000 parts of solvent required for 1 part of solute) in ethanol.

**Drug excipient compatibility studies:**

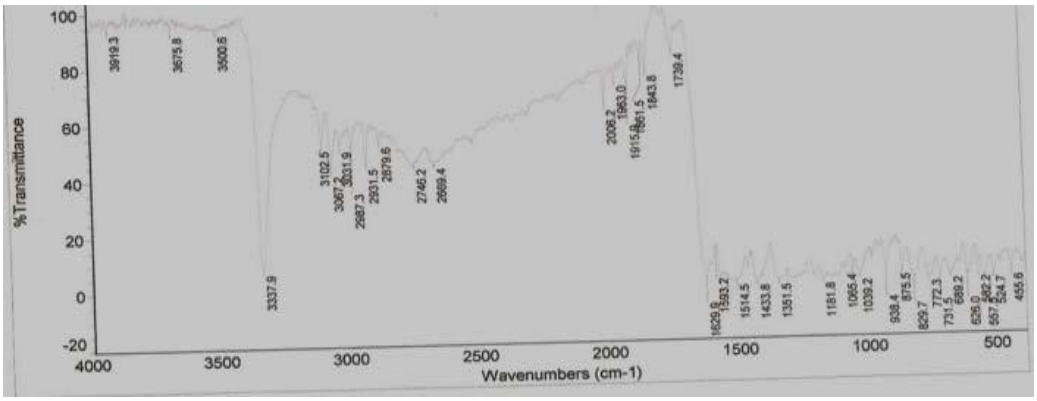



**Fig. 2: FT-IR spectrum of pure drug**

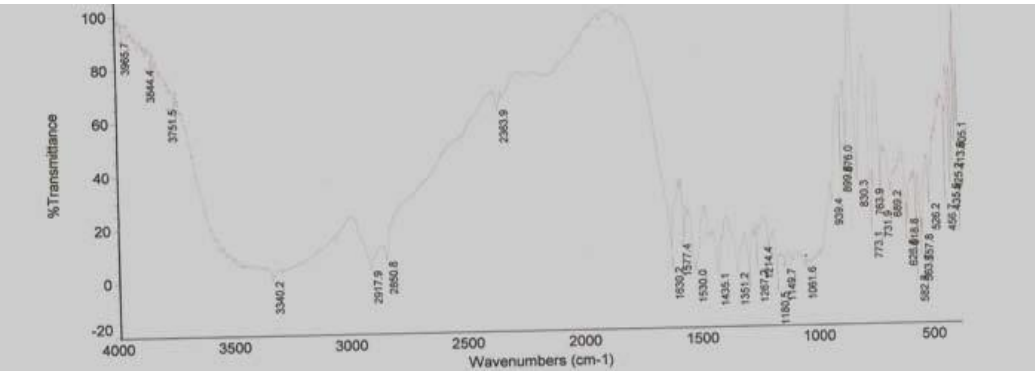



**Fig. 3 : FT-IR spectrum of the physical mixture (before compression)**

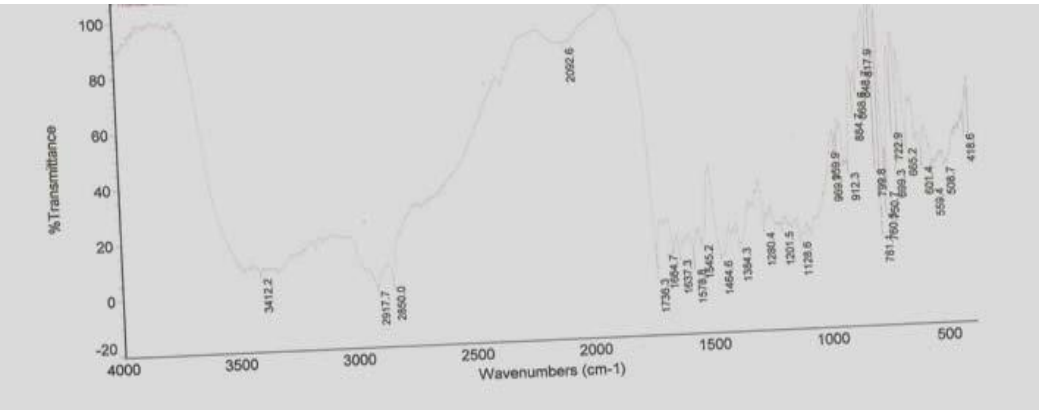



**Fig.4 :FT-IR spectrum of the powdered tablet (F6)**

**Discussion:**

The drug, physical mixture and the final formulation were subjected to IR studies to observe for any incompatibility between the drug and excipients. As the peaks remained unaffected, it can be concluded that there is no incompatibility between the drug and excipients.

**Table 12: Formulations (in mg)**

| S.NO | **Formulation code - INGREDIENTS** | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Salbutamol sulphate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 2 | Microcrystalline cellulose | 92 | 89 | 86 | 92 | 89 | 86 | 92 | 89 | 86 | 86 |
| 3 | Sodium starch glycolate | 3 | 6 | 9 | - | - | - | - | - | - | - |
| 4 | Crospovidone | - | - | - | 3 | 6 | 9 | - | - | - | 9 |
| 5 | Croscarmellose sodium | - | - | - | - | - | - | 3 | 6 | 9 | - |
| 6 | Magnesium fumarate | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 7 | Aerosil | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 8 | Mango flavor | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 9 | Camphor | | | | | | | | | | 3 |

Total weight: 100.3 mg

**Table 13:Evaluation of pre-compression blends:**

| Formulation Code | Angle of Repose(º) | Bulk Density (g/cc) | Tapped Density (g/cc) | Carr's Index | Hausner's Ratio |
|---|---|---|---|---|---|
| F1 | 24.3 | 2.4 | 1.9 | 14.3 | 0.81 |
| F2 | 23.8 | 2.3 | 1.9 | 17.2 | 0.84 |
| F3 | 23.4 | 2.4 | 1.8 | 19.3 | 0.82 |
| F4 | 26.2 | 2.6 | 2.1 | 15.4 | 0.85 |
| F5 | 24.6 | 2.6 | 2.2 | 14.7 | 0.89 |
| F6 | 22.9 | 2.7 | 2.1 | 15.5 | 0.87 |
| F7 | 27.4 | 2.4 | 1.9 | 17.9 | 0.85 |
| F8 | 26.2 | 2.1 | 1.8 | 14.3 | 0.81 |
| F9 | 24.6 | 2.7 | 2.3 | 15.8 | 0.86 |

The prepared granules have excellent flow properties based on the angle of repose values (24-30). Based on the Carr's index and Hausner's ratio, the compressibility index and the flowability of the granules is excellent.

**Table 14: Evaluation of tablets**

| Formulation Code | Weight variation (mg) | Hardness ($kg/cm^2$) | Disintegration time (secs) | Friability (%) |
|---|---|---|---|---|
| F1 | 98±1.3 | 2.4±0.33 | 14 | 0.81 |
| F2 | 99±0.54 | 2.3±0.24 | 14 | 0.69 |
| F3 | 104±1.9 | 3.2±0.46 | 12 | 0.75 |
| F4 | 97±1.4 | 3.0±0.12 | 09 | 0.73 |
| F5 | 98±0.98 | 2.7±0.15 | 08 | 0.76 |
| F6 | 102±1.5 | 3.1±0.17 | 06 | 0.86 |
| F7 | 103±0.8 | 3.0±0.32 | 12 | 0.89 |
| F8 | 97±0.65 | 2.8±0.33 | 10 | 0.91 |
| F9 | 99±1.9 | 2.0±0.19 | 09 | 0.86 |

**Discussion:**

Weight variation was found to be within the limits as per USP-NF 24. Average weight of 20 tablets of all nine formulations was found in the range of 98 to 104mg. Hardness and friability of all the tablet formulations were observed in the range of 2- 3.2kg/cm$^2$ and 0.69 to 0.91 respectively. For all the formulations, with increase in the superdisintegrant concentration from 3-9%, the disintegration time decreased accordingly. The tablets containing polyplasdone exhibit quick disintegration time followed by tablets containing Ac-di-sol and explotab.

**Table 15: Evaluation of tablets**

| Formulation Code | Dispersion time (secs) | Wetting time (secs) | Water absorption ratio (%) | Drug Content (%) |
|---|---|---|---|---|
| F1 | 21 | 12 | 58 | 98.44 |
| F2 | 19 | 10 | 60 | 99.05 |
| F3 | 19 | 10 | 64 | 98.63 |
| F4 | 14 | 9 | 81 | 98.09 |
| F5 | 10 | 6 | 84 | 98.96 |
| F6 | 9 | 5 | 84 | 99.06 |
| F7 | 19 | 10 | 63 | 98.33 |
| F8 | 17 | 9 | 68 | 98.86 |
| F9 | 14 | 9 | 72 | 98.45 |

**Discussion:**

Water absorption ratio (R) value increased with increase in the superdisintegrant concentration (from 3-9 %). Wetting time and water absorption ratio was found in the range of 5-12 secs and 58-84 %, respectively. Drug content of all the formulations was found in the range of 98.33 to 99.06%. Dispersion time decreased with the increase in the superdisintegrant concentration.

**Table 16: Dissolution profiles of ODTs prepared by wet granulation (measured at 275 nm)**

| Time (Min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 28.91±0.12 | 42.24±0.54 | 53.44±0.46 | 32.76±0.14 | 53.96±0.61 | 67.45±0.09 | 34.69±0.35 | 46.25±0.91 | 63.45±0.03 |
| 6 | 34.65±0.45 | 46.86±0.87 | 75.43±0.54 | 36.80±0.73 | 61.97±0.05 | 81.32±0.75 | 44.52±0.04 | 54.22±0.98 | 78.32±0.05 |
| 9 | 46.45±0.09 | 54.67±0.45 | 79.45±0.23 | 50.31±0.91 | 71.65±0.17 | 87.17±0.06 | 50.24±0.25 | 61.97±0.15 | 85.25±0.09 |
| 12 | 50.36±0.08 | 69.70±0.76 | 85.24±0.09 | 60.02±0.05 | 77.48±0.53 | 89.13±0.96 | 54.24±0.24 | 71.85±0.14 | 87.91±0.14 |
| 15 | 63.88±0.05 | 81.82±0.05 | 89.12±0.89 | 69.71±0.37 | 85.22±0.63 | 99.45±0.75 | 63.90±0.17 | 79.41±0.59 | 94.86±0.17 |
| 18 | 75.51±0.33 | 85.95±0.55 | 98.44±0.41 | 77.44±0.04 | 87.45±0.19 | 99.48±0.64 | 69.73±0.13 | 85.24±0.76 | 98.69±0.12 |
| 21 | 81.36±0.17 | 98.45±0.54 | 98.46±0.57 | 79.44±0.96 | 99.24±0.91 | | 81.33±0.12 | 98.13±0.94 | 98.97±0.06 |
| 24 | 85.25±0.19 | 98.72±0.06 | | 85.24±0.84 | 99.32±0.87 | | 87.17±0.54 | 98.24±0.06 | |
| 27 | 98.42±0.23 | | | 99.26±0.72 | | | 98.33±0.33 | | |
| 30 | 98.66±0.44 | | | 99.33±0.71 | | | 98.54±0.04 | | |

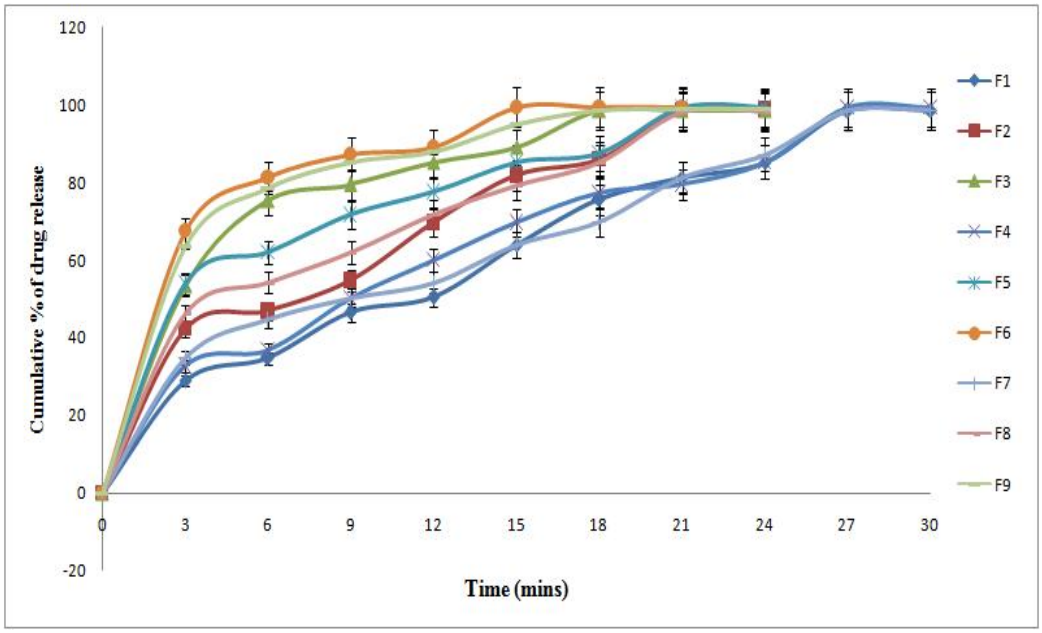
n =**3**

**Discussion:**

*In vitro* dissolution studies of various formulations at different time intervals are shown in fig. 5. The crospovidone formulation (9%) showed the maximum dissolution rate of 99.48% drug release in 18 mins. Ac-Di-Sol (9%) containing tablets released more than 98.66 of the drug in 18 mins and explotab (9%) formulations released more than 98.44% of the drug in 18 mins. This shows that the effectiveness of superdisintegrants was in the order of crospovidone > Ac-Di-Sol > explotab.

**Fig. 5: Dissolution profile of ODTs of Salbutamol sulphate (formulations F1-F9) in pH 6.8**

**phosphate buffer**




**Discussion:**

As the concentration of superdisintegrant increased, the dissolution profile of the tablet improved. This was the same with all three superdisintegrants. The release profiles with crospovidone as the superdisintegrant were much better than that of croscarmellose sodium and sodium starch glycolate. The formulation F6 was found to be the most effective with the best release profile. It contained the superdisintegrant crospovidone in the percentage of 9%.

The same formulation was taken and the tablet was now prepared by changing the method to direct compression and sublimation. The prepared tablets were evaluated for their release profiles and then compared to that of a conventional tablet of Salbutamol sulphate.

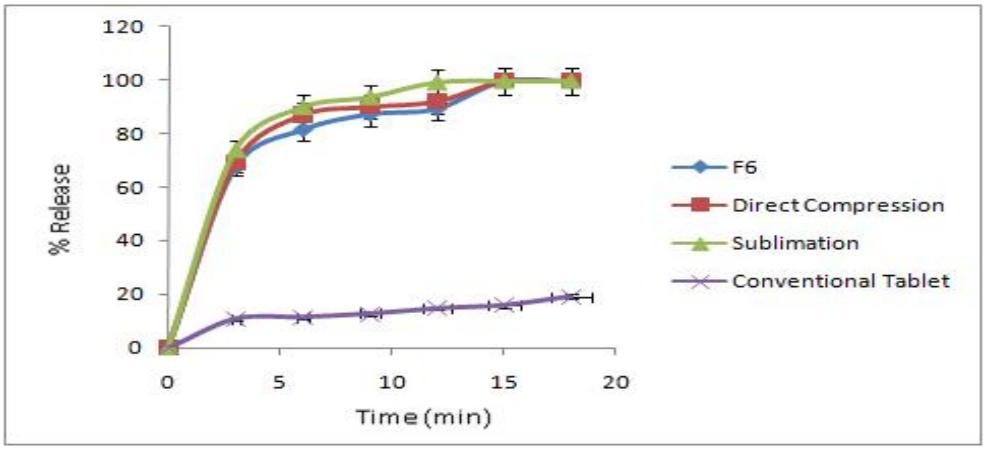
**Table 17: Dissolution profiles of F6 prepared by direct compression and sublimation compared**

**to that of a marketed conventional tablet**

| Time (min) | F6 | Direct compression | Sublimation | Conventional tablet |
|---|---|---|---|---|
| 0 | 00.00 | 00.00 | 00.00 | 00.00 |
| 3 | 67.45±0.15 | 69.06±0.17 | 73.64±0.04 | 10.86 |
| 6 | 81.32±0.17 | 86.84±0.15 | 89.69±0.06 | 11.56 |
| 9 | 87.17±0.33 | 89.98±0.18 | 93.45±0.12 | 12.78 |
| 12 | 89.13±0.44 | 91.95±0.19 | 98.96±0.32 | 14.72 |
| 15 | 99.45±0.32 | 99.48±0.14 | 99.51±0.15 | 15.91 |
| 18 | 99.48±0.31 | 99.49±0.33 | 99.50±0.19 | 19.14 |

The *in vitro* drug release profile F6 was compared with that of the conventional tablet; the conventional tablet released only 19% of the drug in 18mins whereas the F6 formulation (ODT prepared by wet granulation) released up to 99.48%. When the manufacturing method was changed to direct compression and sublimation, there was only a slight variation in the drug release profiles, with sublimation having a better release profile of the three methods.

**Fig.6: Comparative dissolution profiles of F6 prepared by direct compression and sublimation to that of a conventional tablet of Salbutamol sulphate**




**Discussion:**

Disintegration time was given the major importance in selection of the best ODT formulation among all the formulations. For all the formulations, with increase in the superdisintegrant concentration from 3-9%, the disintegration time decreased accordingly. Wicking and capillary action are postulated to be the major factors in the ability of the superdisintegrants to function.

But the tablets prepared with explotab as a superdisintegrant took more time to disintegrate than other superdisintegrants. The tablets containing polyplasdone exhibited quick disintegration time followed by tablets containing Ac-di-sol and explotab. The probable reason for the delayed disintegration and wetting of the tablets might be slow water uptake or more gelling tendency of the Ac-di-sol and explotab.

Bulk densities of various formulations varied from 2.1-2.7g/cc. The angle of repose and the compressibility index values varied from 23° to 27° and 14 to 19 respectively. From these values, it was evident that these blends had excellent flow properties.

Weight variation was found to be within the limits as per USP-NF 24. Average weight of 20 tablets of all nine formulations was found in the range of 98 to 104mg. Hardness and friability of all the tablet formulations were observed in the range of 2- 3.2 kg/cm$^2$ and 0.69 to 0.91% , respectively. Wetting time and water absorption ratio was found in the range of 5-12 secs and 58-84 %, respectively. Water absorption ratio (R) value increased with increase in the superdisintegrant concentration (from 3-9 %).

The *in vitro* disintegration time was rapid with crospovidone containing batches (6-9 secs) and delayed with explotab containing batches (12-14 secs). The rapid disintegration may be due to the rapid uptake of water from the medium, swelling and bursting effect.

*In vitro* dissolution studies of various formulations at different time intervals are reported. The crospovidone formulation (9%) showed the maximum dissolution rate of 99.48% drug release in 18 mins. Ac-Di-Sol (9%) containing tablets released more than 98.66 of the drug in 18 mins and explotab (9%) formulations released more than 98.44% of the drug in 18 min. This shows that the effectiveness of superdisintegrants was in the order of crospovidone> Ac-Di-Sol >explotab.

From the overall observations, formulation F6 containing 9% w/w crospovidone was considered to be the best formulation in the formulations F1-F9 prepared by the method of wet granulation. When the manufacturing method was changed to direct compression and sublimation, there was only a slight variation in the drug release profiles, with sublimation having a better release profile of the three methods.

When compared with a conventional tablet, the conventional tablet released only 19% of the drug in 18mins whereas the F6 formulation prepared by wet granulation released up to 99.48% of the drug within the same time. The fast dissolving tablet of salbutamol sulphate with crospovidone (9%) as the superdisintegrant was found to be an alternative to and better than the conventional tablet dosage form and the rapid dissolving concept in case of salbutamol sulphate could be of great importance in relieving acute asthmatic attacks.

## SUMMARY

Water absorption ratio (R) value increased with increase in the super disintegrant concentration (from 3-9 %). Disintegration time was given the major importance in selection of the best ODT formulation among all the formulations. For all the formulations, with increase in the super disintegrant concentration from 3-9%, the disintegration time decreased accordingly. Wicking and capillary action are postulated to be the major factors in the ability of the super disintegrants to function.

But the tablets prepared with explotab as a super disintegrant took more time to disintegrate than other super disintegrants. The tablets containing polyplasdone exhibit quick disintegration time followed by tablets containing Ac-di-sol and explotab. The probable reason for delayed disintegration and wetting of the tablets might be slow water uptake or more gelling tendency of the Ac-di-sol and explotab.

When the flowing properties of the granules were evaluated, bulk densities of various formulations varied from 2.1-2.7g/cc. The angle of repose and the compressibility index values varied from 23° to 27° and 14 to 19 respectively. From these values, it was evident that these blends had excellent flow properties.

Weight variation was found to be within the limits as per USP-NF 24. Average weight of 20 tablets of all nine formulations was found in the range of 98 to 104mg. Hardness and friability of all the tablet formulations were observed in the range of 2- 3.2 kg/cm$^2$ and 0.69 to 0.91% , respectively. Wetting time and water absorption ratio was found in the range of 5- 12 secs and 58-84 %, respectively.

Drug content of all the formulations was found in the range of 98.33 to 99.06%. The *in vitro* disintegration time was rapid with crospovidone containing batches (6-9 secs) and delayed with explotab containing batches (12-14 secs). The rapid disintegration may be due to the rapid uptake of water from the medium, swelling and bursting effect.

*In vitro* dissolution studies of various formulations at different time intervals are reported. Dissolution profiles were found be better and faster with the increase in the concentration of the superdisintegrant. The crospovidone formulation (9%) showed the maximum dissolution rate of 99.48% drug release in 18 mins. Ac-Di-Sol (9%) containing tablets released more than 98.66 of the drug in 18 mins and Explotab (9%) formulations released more than 98.44% of the drug in 18 min. This shows that the effectiveness of superdisintegrants was in the order of crospovidone> Ac-Di-Sol >explotab.

From the overall observations, formulation F6 containing 9% w/w crospovid one was considered to be the best formulation in the formulations F1-F9 prepared by the method of wet granulation. When the manufacturing method was changed to direct compression and sublimation, there was only a slight variation in the drug release profiles, with sublimation having a better release profile of the three methods. The *in vitro* drug release profile of F6 was compared to that of the conventional tablet; the conventional tablet released only 19% of the drug in 18mins whereas the F6 formulation released up to 99.48%.

Thus it can be summarised that the fast dissolving tablet of salbutamol sulphate with crospovidone (9%) as the superdisintegrant is an alternative to and better than the conventional tablet dosage form.

## CONCLUSIONS

The present study was undertaken to formulate and evaluate fast dissolving tablets of salbutamol sulphate by wet granulation method and comparing with the conventional tablet. The *in vitro* drug release profile F6 was compared with that of the conventional tablet, the conventional tablet released only 19% of the drug in 18mins whereas the F6 formulation released up to 99.48%. Changing the method of manufacture to direct compression from wet granulation resulted in only a slight variation in the amount of drug release. However, tablets prepared by sublimation showed a better release profile.

Thus it can be concluded that the fast dissolving tablet of salbutamol sulphate with Crospovidone (9%) as the superdisintegrant is an alternative to and better than the conventional tablet dosage forms, and the rapid dissolving concept in case of salbutamol sulphate could be of a great importance in relieving acute asthmatic attack.

Future possibilities for improvements in FDTs and drug delivery are bright, but the technology is still relatively new. Thus, it can be concluded that fast dissolving tablets can be prepared with a view of obtaining faster action of the drug and would be advantageous in comparison to the currently available conventional forms. The technique adopted was found to be economical and industrially feasible.

Salbutamol sulphate being a water-soluble drug would be readily available in a dissolved form for rapid oral uptake. The rapid dissolving concept in case of Salbutamol sulphate could be of great importance in relieving acute asthmatic shocks.

# PUBLICATION

**Topic Entitled:** FORMULATION AND *IN VITRO* CHARACTERISATION OF ORO DISPERSIBLE SALBUTAMOL SULPHATE TABLETS

**JOURNAL:** ***International Journal of Advances in Pharmaceutical Research***

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